REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim 1 has been amended to incorporate the limitations of claim 5, as a result of which claim 5 has been cancelled, without prejudice. Claim 6 has been amended in order to be consistent with amended claim 1. Claim 7 has been amended to depend on claim 1, rather than cancelled claim 5. Claim 10 has been amended to replace "(x/x+y) x 100 being an integer of 1-99" with "(x/x+y) x 100 being an integer of 20-65". Support for this amendment is found on page 6, lines 6-7, page 12, lines 14-16 and page 26, line 22 to page 27, line 19 of Applicants' specification.

New claims 16-18 have been added to the application. Support for these claims is found on page 10, lines 10-12, page 27, line 33 to page 28, line 1, Figure 4(b) and the above-mentioned passages of Applicants' specification.

Therefore, no new matter has been added to the application.

The patentability of the present invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Thus, the rejection of claims 1-3 and 9 under 35 U.S.C. § 103(a) as being unpatentable over Baker et al. in view of Barry et al. has been obviated by the claim amendments.

Specifically, as stated above, claim 1 has been amended to incorporate the limitations of claim 5. Claim 5 is not included in the above-rejection. Therefore, amended claim 1, as well as dependent claims 2, 3 and 8 are patentable over the cited combination of references.

The rejection of claims 1-15 under 35 U.S.C. § 103(a) as being unpatentable over Baker et al. in view of Kataoka et al. is respectfully traversed.

The Examiner takes the position that:

> Baker et al. disclose a biosensor system in which colloidal Au nanoparticle is functionalized with two different functional moieties (e.g. streptavidin and protein of interest) which is then contacted with a biosensor surface coated with biotin to form a colloid based biocompatible

> surface (see abstract; Fig. 20 and paragraph [0134]). Baker also disclose BSA and streptavidin coated colloidal Au nanoparticle (i.e. nanoparticle with two different functional moieties) that is bound to biotin coated surface (see Fig. 1C).
>
> ---(omitted)---
>
> Baker et al., however, fail to disclose nanoparticle having functional group or moiety with PEG linker.
>
> Kataoka et al. disclose nanoparticle with a polymer having PEG unit and functional group to attach to nanoparticle and biomolecular targets (see abstract and paragraphs [0004], [0010], [0015], [0023], [0045]). The polymer disclosed by Kataoka et al. also disclose that dispersion stability is improved by using functionalized PEG derivative on metal particles (paragraph [0010]).
>
> Therefore, given the fact that PEG linker is common and known in the art to link functional group or moieties (e.g. binding partner/pair) to nanoparticle, it would have been obvious at the time of the invention to a person of ordinary skill in the art to use PEG linker to link functional group or moieties on nanoparticle in the biosensor system of Baker et al., with the expectation of producing PEG modified nanoparticle based biosensor useful for detection of analytes in a sample by various competitive and noncompetitive assays.

Applicants respectfully disagree with the Examiner's assertion as quoted above. Specifically, Applicants assert that the Examiner's position is based on hindsight, which is improper according to U.S. practice.

In a recent decision, the Court of Appeals for the Federal Circuit (hereafter "Federal Circuit") addressed the issue of hindsight. Specifically, the Federal Circuit stated:

> Most inventions arise from a combination of old elements and each element may often be found in the prior art.... However, mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole... Rather, to establish a *prima facie* case of obviousness based on a combination of elements discussed in the prior art, the Board must articulate the basis on which is concludes that it would have

> been obvious to make the claimed invention... In practice, this requires that the Board "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious." ... This entails consideration of both the "scope and content of the prior art" and "level of ordinary skill in the pertinent art" aspects of the *Graham* test.
>
> When the Board does not explain the motivation, or the suggestion or teaching, that would have led the skilled artisan at the time of the invention to the claimed combination as a whole, we infer that the Board used hindsight to conclude that the invention was obvious.

See In re Kahn, 441 F.3d 977, 986 (Fed. Cir. 2006).

X in the nanoparticle which is shown by formula I of Applicants' invention, i.e., $(X-W^2-PEG-W^1-L)_X-PCL-(L-W^1-PEG-W^2-Y)_y$, is a "residue of a member forming a biological specific binding pair" (a functional group) which includes streptavidin as mentioned in Baker et al. X is, however, covalently bound to PEG to form functional moieties. In this respect, X is different from the functional moieties of Baker et al., wherein streptavidin *per se* constitute functional moieties without the mediation of PEG. Y as another functional moiety (which is selected from the group consisting of C_1-C_6 alkyl, a group or moiety defined above as X, and a group or moiety as defined above as X which is protected, wherein X and Y are not the same simultaneously) is also covalently bound to PEG chain.

Thus, the nanoparticle of formula I as mentioned above (hereinafter referred to as "the invention's particle") is structurally quite different from the functionalized nanoparticle of Baker et al. (hereinafter referred to as "Baker's particle") wherein streptavidin and protein of interest are each directly bound to nanoparticle. Baker's particle is also structurally quite different from the metal fine particle of Kataoka et al. (hereinafter referred to as "Kataoka's particle") which is structurally similar to the invention's particle.

Nevertheless, the Examiner states, in consideration of Kataoka et al., as follows:

> ... given the fact that PEG linker is common and known in the art to link functional group or moieties (e.g. binding

> partner/pair) to nanoparticle, it would have been obvious at the time of the invention to a person of ordinary skill in the art to use PEG linker to link functional group or moieties on nanoparticle in the biosensor system of Baker et al....

Kataoka et al. provide a means to solve a problem. Specifically, paragraph [0006] of Kataoka et al. states:

> However, these conventional ultra fine particles of metal is maintaining its dispersing state by the repulsing forth of surface ions in the medium such as water, therefore, when the substance having opposite electric charge exists, said ultra fine particles of metal are neutralized and cohered, that is, the instability is pointed out as the problem.

Kataoka et al. succeeded in resolving the above-mentioned problem by using PEG chain (see paragraph [0008] of the same) which has high mobility in aqueous medium and which thereby exhibits a repulsing force.

In fact, page 27, lines 2–3 of Applicants' specification states as follows:

> ... it is understood that hardly any lectin-lactose binding occurred with lac 10...

With regard to (X–W^2–PEG–W^1–L) moieties and (L–W^1–PEG–W^2–Y) moieties in formula I, when the former (wherein X is a lactose residue) has a smaller proportion (or a lower density), X is not bound to the surface of lectin which is the other member of a biological specific binding pair, although no PEG chain exists on the surface which carries lectin. This is considered to be caused by the fact that the presence of PEG chain or L–W^1–PEG–W^2–Y chain in the invention's particle prevents the above-mentioned binding.

As suggested by the Examiner, it is understood from Kataoka et al. alone that Kataoka's particle forms a stable dispersion in an aqueous medium by the interaction (repulsing force) of PEG chain among particles, with no aggregation of particles brought about. Thus, PEG chain in Kataoka's particle is not a simple linker as indicated by the Examiner, but plays an important role for the exhibition of repulsing (or repulsive) force. Such a function of PEG chain is considered to be shown also in the invention's particle quite naturally.

In Kataoka et al., their problem as quoted above is very successfully resolved by utilizing repulsing force of Kataoka's particle. As would be seen from the occurrence of the above-mentioned repulsing force, Kataoka et al. neither teach nor suggest assembling a surface which supports the particles, by adhering or binding the particles on a certain surface.

In Baker et al., which provides a means to resolve a problem which is different from the above-mentioned one of Kataoka et al., it is mentioned in paragraph [0013] concerning the assembly of a surface of substrate with use of particles, as follows:

> Fig. 1D depicts various regimes for colloid immobilization that could result from using the strategy delineated above. In surface A, the particles are isolated, but too far apart to be strongly enhancing. In B, the particles are close enough to see the SERS effect, but still isolated (thus retaining the biocompatibility properties of individual particles). Surface C represents a close-packed colloid monolayer, while D represents particle multilayers approximating a bulk surface. The latter surface can be prepared from a monolayer. Our goals are to prepare and characterize surfaces like B, C and D, and to use them to solve a variety of problems in analytical, biological, environmental, clinical and inorganic chemistry.

As stated above, Kataoka's particle forms a stable dispersion in an aqueous medium. Hence, it would have been quite natural for a skilled person to foresee that, even though a surface carrying the particles were successfully assembled, it would only be surface A of Fig. 1D of Baker et al. ("In surface A, the particles are isolated, but too far apart to be strongly enhancing.").

Thus, anyone skilled in the art would have naturally considered that the use of Kataoka's particle in place of Baker's particle in the biosensor system of Baker et al. would fail to give a surface as desired.

Nevertheless, the Applicants' invention produces excellent action and effects.

(i) When "$(x/x+y) \times 100$ is an integer of 20–65" in formula I, e.g., when lac 20 – lac 65 is selected from among the lactose density on particle surface (lac 0, lac 10, lac 20, lac 30, lac 40, lac 50, lac 65) as shown in the section of "Effect of ligand density in the binding" on page 26 of Applicants' specification and in Fig. 3(b), nanoparticles can successfully be bound to a substrate surface which carries lectin. In other words, there is

a suitable ratio of the ($X-W^2-PEG-W^1-L$) moieties to ($L-W^1-PEG-W^2-Y$) moieties in the invention's particle. Kataoka et al., on the other hand, mention or suggest no idea of using two kinds of functional moieties.

(ii) When nanoparticles and substrate surface are made from the same material (e.g., an SPR sensor system wherein Au nanoparticles and a substrate having Au surface are bound to each other), the invention's particle thus produced shows remarkably increased SPR response in comparison with the systems as control (polymer micelle which contains no Au), as mentioned in the present specification, page 25, line 33 to page 26, line 8 (see Fig. 2).

Applicants consider that, with the expected occurrence of repulsing force among the PEG chain-carrying nanoparticles, no one skilled in the art could have foreseen that SPR having particle surface which was assembled with the PEG chain-carrying nanoparticles would give rise to such an increase in response as stated above.

For these reasons, the invention of claims 1-15, and of new claims 16-18 is clearly patentable over Baker et al. in view of Kataoka et al.

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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